Novel HIV PI With High Resistance Barrier and Potential for Unboosted QD Oral Dosing

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Introduction

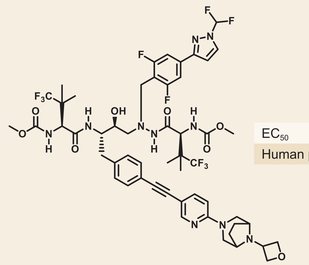
- The HIV protease inhibitor (PI) class remains important based on a low potential to select clinical resistance[1]
- All marketed PIs suffer from high rates of hepatic metabolism
  - None are suitable for qd dosing without pharmacokinetic (PK) boosting with ritonavir or cobicistat
  - Boosting is necessary to reduce frequency of dosing and increase compliance
  - Boosting is associated with drug-drug interactions
- There is an unmet need for an unboosted HIV PI
- Here we describe GS-PI1, a novel, potent PI with a high resistance barrier and exceptional metabolic stability, supporting its potential for use as an unboosted qd agent for use in a single-tablet regimen for the treatment of HIV infection

Methods

- Antiretroviral half-maximal effective concentration (EC_{50}) and Hill-coefficient values were measured in a 5-d multicycle luminescent cell viability assay by measuring protection from cytopathic effect (CPE) in MT4 cells infected with HIV-1_{IIIb} (MOI=0.005)
- PI cross-resistance was assessed at Monogram Biosciences (South San Francisco, CA) against a panel of atazanavir (ATV) and darunavir (DRV) resistance-associated HIV-1 mutants (RAMs)
- Viral breakthrough was assessed in MT2 cells infected with HIV-1_{IIIb} (MOI=0.05) for 3 h and plated in 24-well plates at 2 x 10^5 cells/well
  - Drugs were added 16 h postinfection
  - Every 3–4 d, cells were split 1:5 and monitored for virus-induced CPE over the course of 32 d[2]
- Predicted drug clearance (CL) was measured in human liver microsomes with added cofactors
- Oral and iv PK studies were conducted in rat and dog
- Inhibitory quotient (IQ) defined by the formula IQ(X) = X · EC_{95}

Results

GS-PI1 Structure, Potency, and Metabolic Stability



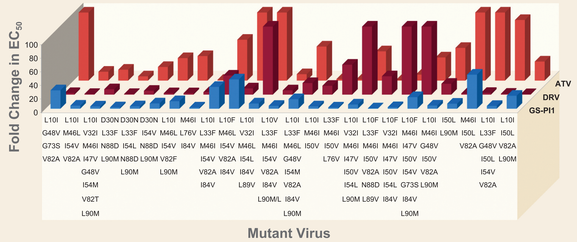
	GS-PI1
EC_{50}	6.8 nM
Human predicted CL	0.05 L/h/kg

Potency of GS-PI1, DRV, and ATV

	GS-PI1	DRV	ATV
K_i, nM	0.060	<0.030	0.035
EC_{50}, nM	6.8	7.2	9.7
Hill-coefficient	5.8	2.9	3.1
EC_{95}, nM	11.4	19.9	25
Protein binding–adjusted EC_{95}, nM	353	42	75

K_i, inhibitory constant.

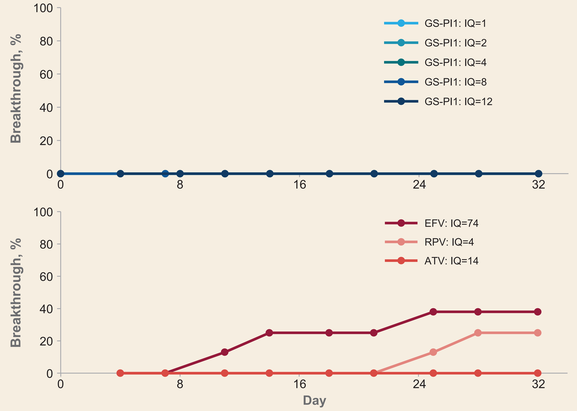
Fold Change vs Wild Type for Clinically Relevant RAMs



Mutant Virus

- GS-PI1 has improved profile vs DRV and ATV against clinical isolates from PI-experienced patients

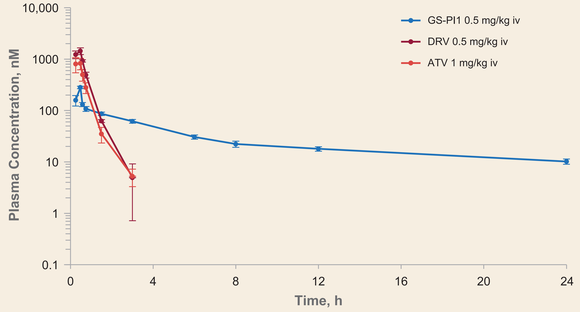
GS-PI1: High-Barrier to Resistance in Breakthrough Assay



- GS-PI1 does not breakthrough at IQ of 1
- EFV and RPV breakthrough at their clinical IQ; ATV does not

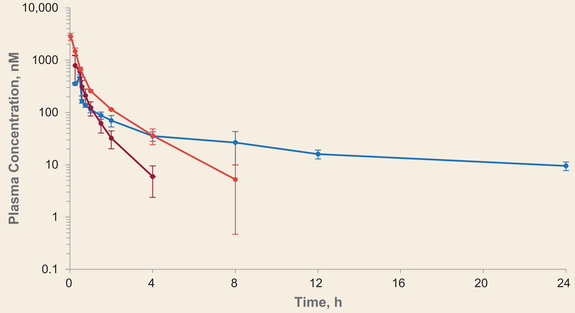
GS-PI1: Long Pharmacokinetic Half-Lives Compared With DRV and ATV

Rat



Rat PK*	GS-PI1	DRV	ATV
CL, L/h/kg†	0.48	2.2	2.7
V_{ss}, L/kg	6.7	0.73	0.87
% F	29	24	38
$t_{1/2}$, h	12.8	0.32	0.37

Dog



Dog PK‡	GS-PI1	DRV	ATV
CL, L/h/kg†	0.47	2.7	1
V_{ss}, L/kg	6.3	0.87	0.9
% F	18	38	48
$t_{1/2}$, h	13.8	0.37	1.3

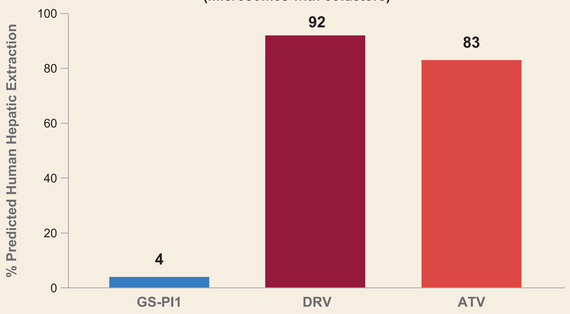
*PK doses: GS-PI1 0.5 mg/kg iv and 2.5 mg/kg oral; DRV 0.5 mg/kg iv and 2 mg/kg oral; ATV 1 mg/kg iv and 5 mg/kg oral; †Predicted CL using hepatic microsomes with added cofactors; ‡PK doses: GS-PI1 0.5 mg/kg iv and 2 mg/kg oral; DRV 0.5 mg/kg iv and 2 mg/kg oral; ATV 2 mg/kg iv and 10 mg/kg oral. F, bioavailability; $t_{1/2}$, half-life; V_{ss}, apparent volume of distribution at steady state.

GS-PI1 Has High Metabolic Stability

Predicted CL
(microsomes with cofactors)

Species	Predicted CL, L/h/kg		
	GS-PI1	DRV	ATV
Rat	0.1	2.8	3.7
Dog	0.45	1.2	1.4
Human	**0.05**	**1.20**	**1.07**

Predicted Human Hepatic Extraction
(microsomes with cofactors)



Conclusions

GS-PI1:

- Is a novel, potent HIV PI
- Has an improved resistance profile, with high activity against DRV and ATV RAMs
- Prevents viral breakthrough in vitro at IQ of 1
- Has long PK $t_{1/2}$ in rat and dog, and is highly stable in human microsomes
- Has the potential for unboosted qd dosing
- Represents a new generation of HIV PIs with potential for combination in an unboosted single-tablet regimen for the treatment of HIV infection

References

1. Baxter JD, et al. J AIDS Clin Res 2016;7:581; **2.** Mulato, A. et al. AIDS Res Hum Retroviruses 2016;32:1237-47.

Acknowledgments

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